SIGNALLING

Filling in the blanks in NF-κB signalling

The mechanism of activation of the kinase complex IKK — which regulates IκB, the inhibitory molecule that controls nuclear factor-κB (NF-κB) activation — during antigen-receptor signalling in T cells has not been well understood to date. But now, a study published in *Molecular Cell* shows that the ubiquitin ligase TRAF6 and the kinase TAK1 have important roles in mediating IKK activation by BCL-10 and MALT1.

The classical pathway for activation of the transcription factor NF-κB in T cells is controlled by the IKK complex. This complex consists of two active kinases (IKK-α and IKK-β) and a regulatory molecule known as IKK-γ or NEMO. Activation of the IKK complex leads to phosphorylation of IκBα, which is ubiquitylated and degraded by the proteasome, allowing NF-κB to translocate to the nucleus and activate gene transcription. It has recently been shown that CARMA1, BCL-10 and MALT1 are important components of this signalling pathway downstream of the antigen receptor and upstream of the IKK complex.

To address the mechanism of IKK activation, the authors developed a cell-free system based on cytosolic extracts, in which IKK is activated by addition of recombinant BCL-10. They initially showed that the ubiquitin-conjugating enzyme complex UBC13–UEV1A has a role in IKK activation. When UEV1A was depleted from cell extracts using Sepharose beads coated with UBC13, addition of recombinant complex to the depleted extracts did not restore IKK activation by BCL-10, indicating that another factor that interacts with UBC13 was also removed. By analysis of the molecules eluted from the UBC13-coated beads, this factor was identified as TRAF6. In addition to TRAF6, RNA interference and dominant-negative experiments showed that MALT1, TRAF2 and the kinase TAK1 are also required for IKK activation. TRAF6 was found to mediate polyubiquitylation of IKK-γ.

Further experiments revealed that a fraction of BCL-10 and MALT1 formed oligomeric complexes and that only these multimerized forms can activate IKK. The authors also showed that oligomerization of TRAF6 activates its ubiquitin ligase activity and that oligomerization of MALT1 is required for TRAF6 oligomerization.

The results in this study support a model of IKK activation in which antigen-receptor signalling results in activation of protein kinase C-θ (PKC-θ), recruitment of BCL-10 to the synapse, followed by oligomerization of BCL-10, MALT1 and TRAF6. TRAF6 then polyubiquitylates itself and other substrates, such as IKK-γ, leading to the activation of TAK1 and the recruitment of TAK1 to the IKK complex. TAK1 can then phosphorylate IKK-β and activate IKK (see figure).

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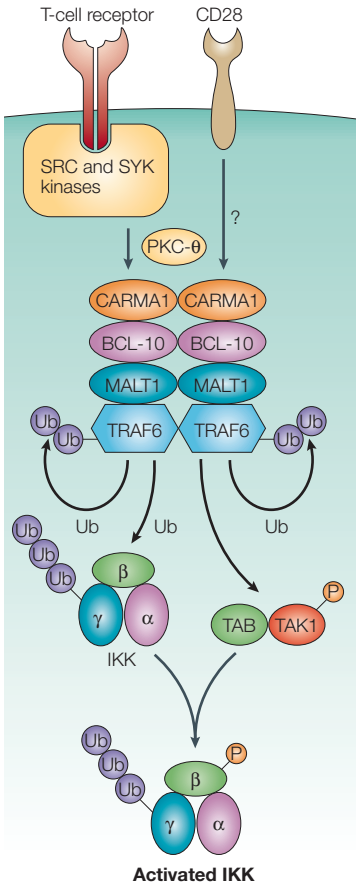

IKK activation in T cells is controlled by an oligomerization–ubiquitylation (Ub)–phosphorylation pathway.

References and links

ORIGINAL RESEARCH PAPER Sun, L. *et al.* The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1 in T lymphocytes. *Mol. Cell* **14**, 289–301 (2004)
FURTHER READING Thome, M. CARMA1, BCL-10 and MALT1 in lymphocyte development and activation. *Nature Rev. Immunol.* **4**, 348–359 (2004)